IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TEXAS
WACO DIVISION

RAVGEN, INC., **Plaintiff,** **v.** **QUEST DIAGNOSTICS INC.,** **Defendant.**	**CIVIL ACTION NO. 6:20-CV-00972-ADA** **JURY TRIAL DEMANDED**

PLAINTIFF RAVGEN, INC.'S REPLY CLAIM CONSTRUCTION BRIEF

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I. The Agent Limitation ('277 Patent, Claims 55, 81; '720 Patent, Claim 1)

A. The Agent Limitation Is Not Indefinite.

Quest argues that the agent limitation is indefinite because the record does not provide express definitions for the terms "cell lysis inhibitor" and "membrane stabilizer" and because the purported breadth and overlap of exemplary regents in those categories allegedly render them undecipherable to a POSITA. Dkt. 49 at 6-8. Quest's arguments were correctly rejected by this Court in the prior *Markman* proceedings.[1] Those indefiniteness theories also conflict with Quest's statements in parallel IPR proceedings and the testimony of its experts, which confirm that the claimed categories were well-known to POSITAs and that the overlap between the categories does not render them indefinite. Quest's theories should therefore be rejected.

As explained in the prior *Markman* proceedings, neither the breadth of the *Markush* categories in the agent limitation nor its functional language render it indefinite. In *BASF Corp. v. Johnson Matthey Inc*., the Federal Circuit rejected arguments that the alleged limitless nature of claimed classes of compounds defined by their function (catalysts) were indefinite because it was the claimed "arrangement of . . . catalysts, rather than the selection of particular catalysts, that purportedly renders the inventions claimed . . . a patentable advance over the prior art." 875 F.3d 1360, 1367 (Fed. Cir. 2017). Similarly, here Quest acknowledges that the "novelty of the asserted patents is using ***known cell-lysis inhibiting agents***" in a new way: "to prepare a sample for diagnostic testing of cell-free DNA/free fetal DNA." Dkt. 49 at 4. Here, as in *BASF*, the alleged

[1] Contrary to Quest's characterization (*id.* at 8-9), the prior defendants, like Quest, argued that the scope of the terms cell lysis inhibitor and membrane stabilizer were unclear based on the breath and overlap of the exemplary agents in the specification. *See, e.g., PerkinElmer* case, Dkt. 55 at 15 (arguing that the "specification provides no limits on [those terms] beyond their overlapping functions and gives so many unrelated and dissimilar examples as to obscure any limits"). Quest's purported due process concerns (Dkt. 49 at 9) are misplaced. Ravgen does not contend that Quest should not be allowed to present claim construction arguments, but rather that Quest's recycled arguments provide no reason to deviate from the Court's prior construction.

breadth of the claimed categories do not render the agent limitation indefinite. 875 F.3d at 1367; *see also PerkinElmer* case, Dkt. 50 at 10-11; Ex. 11 at 20:10-21:14, 27:12-28:11.

Quest's other arguments that a POSITA could not determine the scope of the terms "cell lysis inhibitor" and "membrane stabilizer" are also unsupported by law. Quest does not—and cannot—cite to any case holding that definiteness requires an express definition in the specification or technical dictionaries.[2] Rather, the relevant inquiry is whether the "claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc*., 572 U.S. 898, 910 (2014). Nor does Quest cite any legal support for its theory that overlap between the categories in a *Markush* group necessarily renders the scope of the categories unbounded.[3] Quest's own representations to the PTAB and its experts' testimony confirm that the intrinsic record provides ample guidance regarding the scope of the claim terms and that the overlap between the categories does not prevent a POSITA from determining whether particular substances fall within their scope.

First, a POSITA would understand the plain language of "cell lysis inhibitor," in view of the intrinsic record, to encompass chemical substances that prevent or reduce the rupture of cell membranes and release of cellular contents by protecting or preserving the structural integrity of the cells. Dkt. 46-13 ¶ 51. That well-known category of substances is often referred to as

[2] Quest relies on Dr. Johnson's opinions that "cell lysis inhibitor" and "membrane stabilizer" have never been "term[s] of art used in the field" because selected dictionary excerpts do not define those terms. Dkt. 49 at 6-7, citing Dkt. 49-1 ¶¶ 42, 46. Notably, those excerpts also lack definitions for the undisputed term of art "cross-linker," belying Dr. Johnson's inference regarding the other claim terms. Van Ness Reply Decl. (filed herewith) ¶¶ 60-61. Further, Dr. Johnson admitted that he performed no literature searches or other research before drawing his conclusion that those terms have never been used in the field. Ex. 14 at 63:22-71:9. In fact, Dr. Van Ness has identified patents and publications in the field that use those terms to refer to the same reagents listed as examples in the specifications. Van Ness Reply Decl. ¶¶ 62-63.

[3] When supported by intrinsic evidence, categories in a *Markush* group may overlap. *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1363 (Fed. Cir. 2016).

"fixatives." Van Ness Reply Decl. ¶¶ 22-23. Indeed, Quest and its experts use the term "cell lysis inhibitors" interchangeably with "reagents for fixing" and "fixatives," and admit that such reagents were well-known for preventing cell lysis. Quest admits in its IPRs that at the time of the invention, there were "***many known cell lysis inhibitors***," and describes the well-understood characteristics of such "fixatives." *See, e.g.,* Ex. 12 at 19, 17-18 ("[R]esearchers have identified many reagents for fixing (i.e., preventing lysis of) WBCs [white blood cells]. Since at least the 1890s, formaldehyde has been used as a fixative. Once a WBC is fixed, the cellular content including the DNA is 'locked' inside the fixed cell. When formaldehyde is used on a WBC, it preserves its structure and prevents DNA from leaking out.") (internal citations omitted); Ex. 13 ¶¶ 74-76. In its responsive brief, Quest similarly admits that "researchers had identified ***many reagents*** for preventing lysis of white blood cells," including formaldehyde, "a ***known fixative***" that "***preserves the structure of cells***." Dkt. 49 at 3. Quest's expert, Dr. Johnson, also explained that by using a "fixative," such as formaldehyde, "DNA in the white blood cells is locked inside the cell." Dkt. 49-1 ¶ 25. At his deposition, Dr. Johnson admitted that "fixative is a term of art[, a]nd it refers to reagents that preserve the internal and external structure and integrity of cells" and thus "lock[s] the cellular DNA inside the cell." Ex. 14 at 102:14-18, 103:25-104:6, 103:11-18.

The intrinsic record confirms the plain meaning of the term "cell lysis inhibitor." For example, the prosecution history uses the term "fixative" and "cell lysis inhibitor" interchangeably to refer to the well-known category of chemical reagents that "fix[] (i.e. inhibit[] the cell lysis of WBCs)" by "preserving the structure of a biological molecule" (*e.g.* a cell). Ex. 15 at 35. That office action further notes that paraformaldehyde, formaldehyde and glutaraldehyde were known fixatives that "act by crosslinking proteins, with the resulting crosslinked products stabilizing the cellular ultrastructure." *Id.* (citing Kiessling reference). The specifications confirm the same plain

meaning by describing experiments using known fixatives (formaldehyde and glutaraldehyde) and noting that any other "agent that prevents the lysis of cells or ***increases the structural integrity of the cells***" could also be used. '277 Patent at 91:46-49, 223:1-7; Van Ness Reply Decl. ¶ 27. The specifications also list as exemplary cell lysis inhibitors reagents that were well-known fixatives. *Id.* ¶¶ 28-29. As Dr. Van Ness explains, the exemplary "cell lysis inhibitors" in the specifications confirm that that term refers to chemical reagents that inhibit cell lysis using a common mechanism: fixing (*i.e.,* preserving the structure of) cells by crosslinking polymers. *Id.* ¶ 30. In fact, Quest admits that the exemplary cell lysis inhibitors in the specification are all cross-linkers. Dkt. 49 at 7.[4] But contrary to Quest's assertions, the scope of the term cell lysis inhibitor (*i.e.* fixative) is not coextensive with cross-linker. Rather, as Dr. Johnson admits, "[f]ixatives can include cross-linkers, but do not, by definition, have to be a cross-linker. Cross-linkers can be a fixative, but not all cross-linkers are considered to be fixatives." Ex. 14 at 132:13-133:10.

The intrinsic record also confirms the scope of cell lysis inhibitor by explicitly identifying certain classes of chemical substances that are not cell lysis inhibitors. For example, Dr. Johnson admits that cell lysis can occur during clotting and that anticoagulant chelators like EDTA are "reagent[s] that prevent[] the clotting of blood." Ex. 14 at 150:13-20. However, such reagents are not fixatives—they do not preserve the structure of cells—and therefore are not "cell lysis inhibitors." Van Ness Reply Decl. ¶ 35. The intrinsic record confirms that such anticoagulant chelators are not cell lysis inhibitors. Ex. 3 at 33 ("[T]he assertion by the Office that EDTA is a cell lysis inhibitor is simply incorrect. Applicant asserts that EDTA is not an 'agent that inhibits

[4] Dr. Johnson states that the specification identifies as cell lysis inhibitors: "formaldehyde, and derivatives of formaldehyde, formalin, glutaraldehyde, and derivatives of glutaraldehyde and a long list of cross-linkers." Dkt. 49-1 ¶ 44. He testified that the listed aldehydes and their derivatives are all fixatives that inhibit lysis by crosslinking. Ex. 14 at 136:19-137:5, 104:22-105:8.

cell lysis.' Rather, EDTA is a well-known chelator of calcium and magnesium."); Ex. 16 at 3; '277 Patent at 31:52-56; Van Ness Reply Decl. ¶¶ 35-37.[5] As Dr. Johnson admitted, Example 4 in the specifications describes samples treated with EDTA alone as a control representing "the ***absence . . . of inhibitors of cell lysis***" for comparison against samples treated with EDTA and formalin (described as "the presence . . . of inhibitors of cell lysis"); Ex. 14 at 155:22-156:12, 157:4-158:9. He also acknowledged the prosecution history evidence demonstrating that anticoagulant chelators are outside the scope of "cell lysis inhibitor" as used in the patents. *Id.* at 176:4-12. However, Dr. Johnson improperly ignored those disclosures in concluding that the intrinsic record provides no guidance as to the scope of "cell lysis inhibitor." *Id.* at 42:6-43:5, 171:22-172:23, 174:20-175:15, 199:12-200:17. Based on the plain meaning of cell lysis inhibitor as confirmed by the extensive guidance in the intrinsic record, a POSITA would thus understand that term to refer to the well-known, bounded category of chemical reagents that prevent or reduce cell lysis by preserving the structural integrity of cells.

Second, a POSITA would understand the scope of the claim term "membrane stabilizer" in view intrinsic record. Quest asserts that term's scope is unclear because it is undefined and the examples listed in the specifications share no common structure or mechanism. Dkt. 49 at 7-8. That argument ignores that the claim language itself would be easily understood by a POSITA to refer to a bounded category of chemical reagents that inhibit cell lysis using a particular mechanism: stabilizing the membranes of cells. Van Ness Reply Decl. ¶¶ 38-39. In fact, Dr. Johnson confirmed that a POSITA would understand the plain language to require agents that contribute to the stability of cell membranes. Ex. 14 at 144:4-16, 147:9-22. Dr. Johnson further

[5] Quest's assertion that the exclusion of EDTA and similar chelating anticoagulants are "arbitrary disclaimers during litigation" (Dkt. 49 at 15) is incorrect and ignores the specifications and the prosecution history that unequivocally confirm that EDTA is not a claimed agent.

admitted that reagents that stabilize cell membranes are a particular subcategory of the reagents capable of inhibiting cell lysis. *Id.* at 144:18-145:13.[6] As he testified, "not all chemical compounds that reduce cell lysis do so by stabilizing the mem[branes]," and not all reagents that stabilize cell membranes will necessarily inhibit cell lysis. *Id.* at 148:14-17, 146:9-147:5.

Quest argues that a POSITA would not be able to determine the scope of the terms "cell lysis inhibitor" and "membrane stabilizer" because certain chemical substances (formaldehyde and formalin) are included in the specifications' lists of exemplary cell lysis inhibitors and membrane stabilizers and are also known cross-linkers.[7] Dkt. 49 at 7. However, in Quest's IPRs, Quest and its expert were able to apply those terms to a prior art reagent that fell into multiple categories. Quest's expert determined that a prior art reagent system was "***both a 'membrane stabilizer' and 'cell lysis inhibitor'***" because the reagent system "will 'preserve white cell morphology,' 'fix white blood cells,' and 'preserve white cell membrane integrity.'" Ex. 13 ¶ 140.[8] That analysis confirms that a POSITA can easily apply the terms "cell lysis inhibitor" and "membrane stabilizer" according to their plain meanings described above despite any overlap.

B. The Agent Limitation Is Not Subject To 35 U.S.C. § 112 ¶ 6.

Quest cannot overcome the presumption that the agent limitation should ***not*** be construed

[6] Dr. Johnson does not dispute that the exemplary membrane stabilizers are capable of inhibiting cell lysis using the mechanism of stabilizing cell membranes. Ex. 14 at 109:17-111:10, 112:9-18.
[7] Dr. Johnson's alleged confusion stems from the fact that the specifications do not list formaldehyde as an exemplary cross-linker. Ex. 14 at 122:5-14. But Dr. Johnson admits that the specifications' lists are exemplary—they do not include all possible cross-linkers, and thus do not change the clear scope of that term of art. *Id.* at 127:17-24; Van Ness Reply Decl. ¶ 32.
[8] Quest's attempts to justify its inconsistent positions in its IPRs are unconvincing. Dkt. 49 at 9-10. The excuse that Quest only pointed to formaldehyde in the prior art is contradicted by its representation to the PTAB that "[f]ormaldehyde was one of ***many known cell lysis inhibitors.***" Ex. 12 at 19. And that Quest was not permitted to raise indefiniteness in its IPRs negate its arguments to the PTAB that the claimed categories were well-known and could be applied to prior art. *Samsung Elecs. Am., Inc. v. Prisua Eng. Corp.*, 948 F.3d 1342, 1355 n.5 (Fed. Cir. 2020) (the PTAB's limited authority does not change that "a claim cannot be both indefinite and anticipated").

as means plus function subject to § 112 ¶ 6. Its arguments that "agent" is a nonce word and that the limitation fails to recite structure lack legal support and improperly ignore the plain language, the context of the limitation in the claims, and the intrinsic record. Moreover, those arguments once again directly conflict with Quest's statements to the PTAB and its experts' testimony.[9]

Quest's assertion that the term "agent" is a nonce word improperly ignores that term's context in the claims and the intrinsic record.[10] Quest asserts that the claimed agent "is not even limited to a chemical structure" based solely on an extrinsic dictionary definition of "agent." Dkt. 49 at 12. But that reading cannot be squared with the claim language. The claims require that the claimed agent be included in the biological sample[11] and that the agent be selected from three categories of chemical reagents. *See, e.g.*, '277 Patent, Claim 55 ("***sample comprises*** free fetal DNA and ***an agent*** that inhibits lysis of cells . . . selected from the group consisting of ***membrane stabilizer, cross-linker, and cell lysis inhibitor***"); Van Ness Reply Decl. ¶¶ 18, 51, 52. Dr. Johnson admits that the claimed cell lysis inhibitors, membrane stabilizers and cross-linkers are chemical "reagents," meaning chemicals in solution that are used in experimental procedures. Ex. 14 at 106:24-107:4, 121:24-122:4, 113:19-24; Dkt. 49-1 ¶¶ 28, 30. Dr. Johnson's assertion that there is "no language in the claim to suggest that centrifugation would not be considered to be an agent" shows that Quest's position conflicts with the plain claim language. Ex. 14 at 118:23-119:4.

Quest's theory—that the agent limitation covers all possible chemical, mechanical, and

[9] Quest blames its new means-plus-function theory on Ravgen's infringement contentions. Dkt. 49 at 16. But theories of infringement by accused products have no bearing on whether a POSITA would understand the agent limitation, in view of the claims and specification, to recite structure.
[10] Notably, Quest does not cite a single case finding that the term "agent" is a nonce word and fails to address the cases cited in Ravgen's Opening Brief construing the term "agent" in patents relating to biology without invoking § 112 ¶ 6. *See* Dkt. 46 at 8, n.6.
[11] In fact, Quest acknowledges that the novelty of the Patents-in-Suit was the addition of the claimed agent to a sample. Dkt. 49 at 4, citing RAVGEN-00015490 ("the key limitation i.e. wherein an agent that impedes cell lysis is added to the sample.").

environmental means for inhibiting cell lysis—also conflicts with the specifications and dependent claims. For example, while the specifications disclose means for preventing lysis that do not involve using a chemical agent, (*e.g.*, modifying the centrifugation protocols), such means are claimed separately from the agent limitation. *See, e.g.,* '277 Patent, Claims 94, 95; Van Ness Reply Decl. ¶ 53. In fact, as explained above, the agent limitation does not even include every conceivable chemical reagent that could result in less lysis.[12] *See, e.g.,* '277 Patent, Claim 132 (claiming plasma, which requires the use of an anticoagulant reagent, separately from the claimed categories of reagents); Ex. 14 at 85:6-10, 150:13-20; Van Ness Reply Decl. ¶¶ 55-57.

Even if agent were a nonce word, the claims recite particular structures for performing the claimed function. As explained above, each of the claimed categories is a class of chemical substances that inhibits cell lysis using a particular mechanism. For example, Quest admits that cross-linker is a term of art and that cross-linkers inhibit cell lysis through a common mechanism: cross-linking. *See, e.g.,* Dkt. 49 at 12, 14; Dkt. 49-1 ¶ 50. Similarly, Quest admits that the class of membrane stabilizers does not include every chemical substance that inhibits cell lysis, but rather is limited to the particular category of reagents that inhibit lysis using a common mechanism: stabilizing cell membranes. *See, e.g.,* Dkt. 49 at 12, 14. Finally, as explained above, the intrinsic record confirms that not all chemical substances that may result in a reduction in lysis are "cell lysis inhibitors," but rather that term refers to particular chemical reagents (*i.e.*, fixatives) that

[12] Quest mischaracterizes Ravgen's position as "attempting to claim ***all*** chemical substances that perform the recited function." Dkt. 49 at 13. In any event, the cases that Quest cites do not support the conclusion that terms covering chemical reagents that perform a claimed function lack structure. Two involved terms that recited "means" and no structure and thus § 112 ¶ 6 applied. *Blackboard, Inc. v. Desire2Learn Inc.*, 574 F.3d 1371, 1385 (Fed. Cir. 2009); *J & M Corp. v. Harley-Davidson, Inc.*, 269 F.3d 1360, 1367 (Fed. Cir. 2001). And the third involved a purely functional term to be performed by software. *Advanced Ground Info. Sys., Inc. v. Life360*, Inc., 830 F.3d 1341, 1348 (Fed. Cir. 2016).

prevent cell lysis using a common mechanism: preserving the structural integrity of cells to lock DNA inside. Because the agent limitation does not cover "every conceivable way or means to perform the function," the term "agent" is not a nonce word that is equivalent to "means for." *See Multilift Wellbore Tech., Ltd. v. ESP Completion Techs., LLC*, No. CV H-17-2611, 2018 WL 925062, at *13 (S.D. Tex. Feb. 16, 2018).[13] Thus, the agent limitation is not subject to 112 ¶ 6.

II. The Isolating And Detecting Limitation ('720 Patent, Claim 1)

Quest's argument that the isolating and detecting limitation is indefinite is premised on its incorrect assumption that, in the claimed "method for detecting ***a*** free nucleic acid," both "isolating free nucleic acid" and "detecting . . . ***the*** free nucleic acid" must refer to the same nucleic acid. Because Quest's theory conflicts with the record and is unsupported by law, it should be rejected.

First, Quest incorrectly argues that because "isolating free nucleic acid" precedes "detecting . . . the free nucleic acid" they ***must*** refer to the same nucleic acid. "[T]he patentee's mere use of a term with an antecedent does not require that both terms have the same meaning." *Microprocessor Enhancement Corp. v. Texas Instruments Inc.*, 520 F.3d 1367, 1375 (Fed. Cir. 2008). Here, "free nucleic acid" "is not surrounded by uniform language that requires a single interpretation of the term . . . . Rather, the appropriate meaning [] is readily apparent from each occurrence in context." *See id.* at 1376–77. As shown below, "free nucleic acid" appears three times, in two different contexts. Twice, it is particularized by **an article** in the **detecting** context,

[13] *Diebold Nixdorf, Inc. v. Int'l Trade Comm'n.*, is distinguishable. Dkt. 49 at 12, citing 899 F.3d 1291, 1298 (Fed. Cir. 2018). In that case, the claims did not recite any structure for the term "cheque standby unit;" "[n]one of the dependent claims add limitations that either describe particular structural features or flesh out whether the term has a particular structural meaning;" and "the written description does not include any examples of what structures or class of structures fall within the definition" of that term. 899 F.3d 1298-99. To the contrary, here, the claims recite three categories of chemical reagents, the dependent claims narrow those categories to particular substances, and the specifications lists exemplary reagents in each category and describe experiments using such reagents to practice the claims. Van Ness Reply Decl. ¶¶ 50-58.

and once it is not particularized by an article in the **isolating** context:

> [a] method for **detecting a free nucleic acid**, wherein said method comprises: (a) **isolating free nucleic acid** from a non-cellular fraction of a sample. . . and (b) **detecting** the presence or absence of **the free nucleic acid**.

'720 Patent, Claim 1. A POSITA would understand from that context and from the specification that: (1) "isolating free nucleic acid" encompasses isolating a mixture of free nucleic acids, and (2) that "detecting" ***a/the*** free nucleic acid encompasses detecting the presence or absence of a particular free nucleic acid in the isolated nucleic acid.[14] Dkt. 46-13 ¶¶ 74-78. Because the patent "puts the reader on notice that the term [free nucleic acid] . . . has different meanings . . . depending on its context . . . the term must be read to correspond to the only plausible meaning in each context." *See Pitney Bowes, Inc. v Hewlett-Packard Co.*, 182 F.3d 1298, 1311 (Fed. Cir. 1999).

Second, Quest and its experts confirm that the alleged uncertainty regarding the isolating and detecting limitation is manufactured for this litigation.[15] In fact, Dr. Johnson admitted that in "***any*** method that sought to ***detect a particular*** free nucleic acid like free fetal nucleic acid, the first step would be ***isolating*** that whole mixture . . . ***of all of the free nucleic acid*** from the sample." Ex. 14 at 190:5-15; *see also id.* at 189:9-190:3, 81:16-83:3, 191:22-192:4. Quest likewise understood and applied the plain and ordinary meaning its IPR petition to argue that claim 1 is obvious over a prior art that allegedly "teaches isolating free nucleic acid (*i.e.*, free DNA) . . . and detecting cffDNA" (i.e. free ***fetal*** DNA). Ex. 17 at 25; *see also id.* at 13, 14, 19, 31. Because the record does not support Quest's interpretation as allegedly "requir[ing] the impossible" (Dkt. 49 at 17), the Court should reject that interpretation that would render the claim indefinite.

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[14] Quest's analogy to *Trustees of Columbia Univ.* (Dkt. 49 at 17-18) fails because a POSITA would understand that the presence or absence of a particular free nucleic acid can be detected from isolated free nucleic acid. Van Ness Reply Decl. ¶ 67.

[15] Quest points to: (1) an embodiment in the specification and (2) a statement in the prosecution history that its expert did not even find relevant. *See* Ex. 14 at 44:9-18. Quest provides no support that claim 1 even covers that embodiment or that, even if covered, it renders the claim indefinite.

Dated: August 25, 2021 By: /s/ *Kerri-Ann Limbeek* (*pro hac vice*)

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that all counsel of record who are deemed to have consented to electronic service are being served with a copy of this document and all attachments thereto via the Court's CM/ECF system on August 25, 2021.

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